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Asymmetric Synthesis of Benzilic Acid Analogues Using 8-Phenylmenthol as a Chiral Auxiliary

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Abstract: Our program on the synthesis of ^{18}F-labeled muscarinic receptor ligands required the preparation of chiral fluoroalkyl benzilic acids. An enantioselective synthesis of substituted benzilic acids was achieved using 8-phenylmenthol as the chiral auxiliary. Grignard addition to the *si* face of 8-phenylmenthyl benzoylformate 7 proceeded with high selectivity. The results of the chiral induction support assignments of the chirality of benzilic acids previously resolved by crystallization. The method was used to synthesize (R)-quinuclidinyl-(R)-(4-iodo)benzilate, which proved identical to an authentic sample. In addition, the method allows the preparation of (R)- and (S)-fluoroethyl benzilic acids in a stereoselective manner.

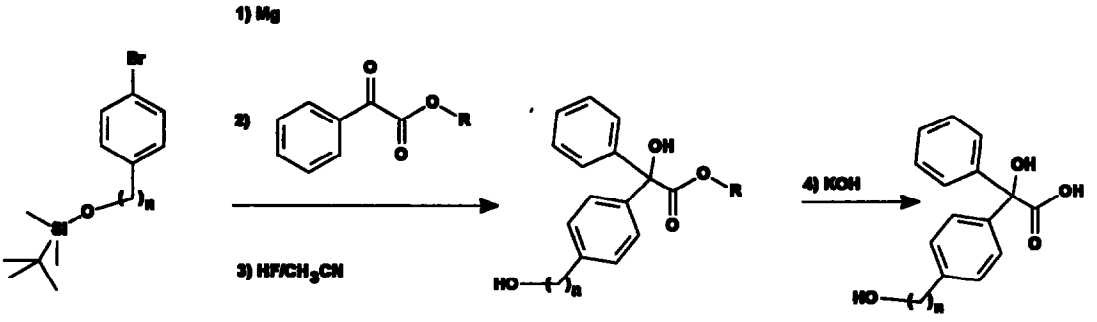
INTRODUCTION

(R)-Quinuclidinyl-(R)-iodobenzilate [(R,R)-IQNB, 22] has been labeled with ^{123}I and ^{125} I as an agent for *in vitro* assays as well as *in vivo* imaging with single photon emission computed tomography[1]. This compound has two stereogenic centers. The (R)-enantiomer of quinuclidinyl benzilate displays significantly higher anticholinergic activity than does the (S)-enantiomer.[2] The configuration at the bis-benzilic center has an interesting consequence. The binding affinity of (R,R)-IQNB (K_a 8.93 ± 1.36 x 10^9 M^{-1}) is 3 fold higher than its diastereomer, (R)-quinuclidinyl-(S)-iodobenzilate [(R,S)-IQNB], (K_a 2.90 ± 0.45 x 10^9 M^{-1}). However the dissociation rate of (R,S)-IQNB (0.0654/min) is 13 times faster than that of (R,R)-IQNB (0.0049/min)[3,4]. In contrast to this advanced knowledge on the biology of these two diastereoisomers, the assignment of configuration has not been firmly established. The configurational assignment at the bis-benzylic center is based on earlier literature that reported higher muscarinic activity for 2-substituted-2-hydroxy phenyl acetates.[5]

As part of our program on the synthesis of ^{18}F-labeled muscarinic receptor antagonists based on the pharmacophore, quinuclidinyl benzilate, we wished to prepare fluoroalkyl substituted QNB derivatives in a stereoselective manner. We sought to prepare chiral derivatives of benzilic acid using 8-phenylmenthol as a chiral auxiliary.[6] This report presents the results of our synthesis of homochiral benzilic acids. In addition, the results support the assignment of the absolute configuration of (R,R)-IQNB.

RESULTS AND DISCUSSION

Resolution by crystallization. Previous literature reported that the crystallization of the quinidine salt of 4-nitrobenzilic acid provides the dextrorotatory enantiomer of the benzilic acid.[3] This enantiomer was assigned the (R)-configuration based on the higher affinity of IQNB prepared from this dextrorotatory enantiomer as opposed to the levorotatory enantiomer.[5] Subsequently, the mother liquors were treated to recover the nitrobenzilic acid enriched in the levorotatory enantiomer. Crystallization of this mixture as the quinine salt provides the levorotatory enantiomer, which is assigned the (S)-configuration. In a similar approach, we prepared both 4-hydroxyethylbenzilic acid **5** and 4-hydroxypropylbenzilic acid **6** and resolved a single enantiomer by crystallization as the quinidine salt (Scheme 1). The Grignard derived from a silyl protected p-(bromophenyl)alkyl alcohol was added to an ester of benzoylformic acid. The resulting benzilate derivative was hydrolyzed to the corresponding benzilic acid. The benzilic acid derivative was then resolved by successive crystallizations as the quinidine salt. The stereogenic center is assigned as (R) based on analogy with the results of Cohen[3] and from the results of the enantioselective route discussed below. In our hands, the corresponding (S)-enantiomer would not crystallize as the quinine salt. The optical purity of these benzilic acid derivatives could be assayed by chiral HPLC on a Chiral Pak WH column. The (R)-enantiomer elutes prior to the (S)-enantiomer (Table 1).

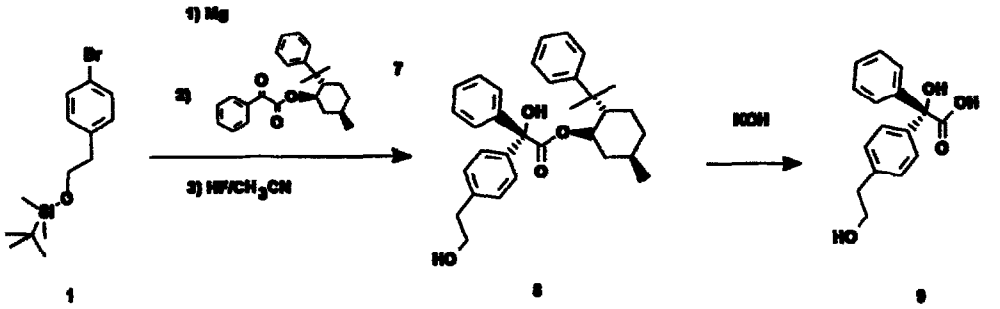


Scheme 1

Enantioselective synthesis of benzilic acids.

Synthesis of the (S)-benzilic acids. Whitesell has shown that methyl magnesium bromide adds to the *si* face of 8-phenylmenthyl benzoylformate and produces the (R) stereogenic center.[7] The assignment of configuration was made following reduction to the known homochiral diol. To prepare 8-phenylmenthyl benzoylformate, benzoylformic acid was converted to the acid chloride using α,α-dichloromethyl methyl ether[8] and added to 8-phenylmenthol. (S)-Hydroxyethyl benzilic acid **9** was prepared by treating 8-phenylmenthyl benzoylformate **7** with 4-[1-(t-butyldimethylsilyloxy)ethyl] phenyl magnesium bromide (Scheme 2). Following

the precedent of Whitesell, the Grignard reagent will add to the *si* face of the keto ester. Because the substituted aromatic ring is of higher priority than the phenyl ring, the resulting stereogenic center has the (S)-configuration. Subsequent removal of the silyl protecting group utilizing HF in acetonitrile provided the desired hydroxyethyl benzilate 9[9].



Scheme 2

Table 1. Retention times of benzilic acids on Chiral Pak WH (4.6 x 50 mm: 10 % MeOH, 90 % 1mM $CuSO_4$, 1 mL/min, Column Temperature 50 °C

Benzilic Acid	Retention Time (min)
(9) (S)-hydroxyethyl	13.9
(5) (R)-hydroxyethyl	10.4
(6) (S)-hydroxypropyl[a]	16.6
(6) (R)-hydroxypropyl	12.3
(12) (S)-fluoroethyl	15.5
(16) (R)-fluoroethyl	13.0

a Retention time determined from the racemate.

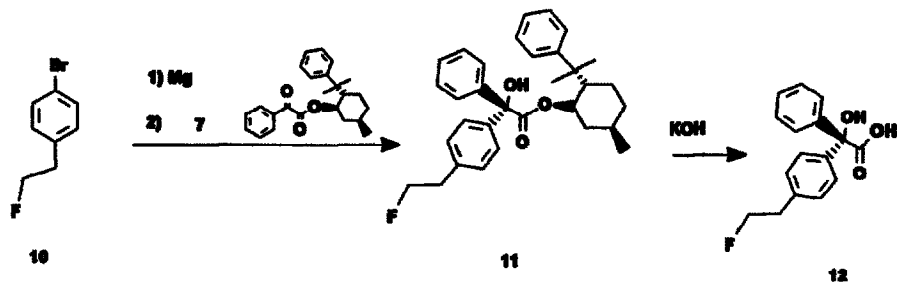
The diastereomers from this Grignard addition could be separated on reversed phase high performance liquid chromatography (HPLC). The HPLC retention times are recorded in Table 2. The addition product obtained at an initial reaction temperature of -78 °C shows a diastereomeric impurity of less than 5 %. If the reaction has an initial temperature of 25 °C, the diastereomeric impurity is about 7 percent. If the reaction utilizes the organolithium compound, the diastereomeric impurity increases to about 15 %. The effect of temperature and organometallic species on the selectivity of the addition is consistent with that previously reported by Whitesell.[10]

Table 2. HPLC retention time for 8-phenylmenthyl ester derivatives of benzilic acids. Beckman ODS (C-18, 4.6 x 250 mm)

Benzilate	CH_3CN %	WATER %	flow rate (mL/min)	retention time min
(8) (S)-hydroxyethyl	65%	35 %	1.5	21.1
(8)[a] (R)-hydroxyethyl	65 %	35 %	1.5	22.1
(11) (S)-fluoroethyl	70 %	30 %	2	35.2
(15) (R)-fluoroethyl	70 %	30 %	2	36.1

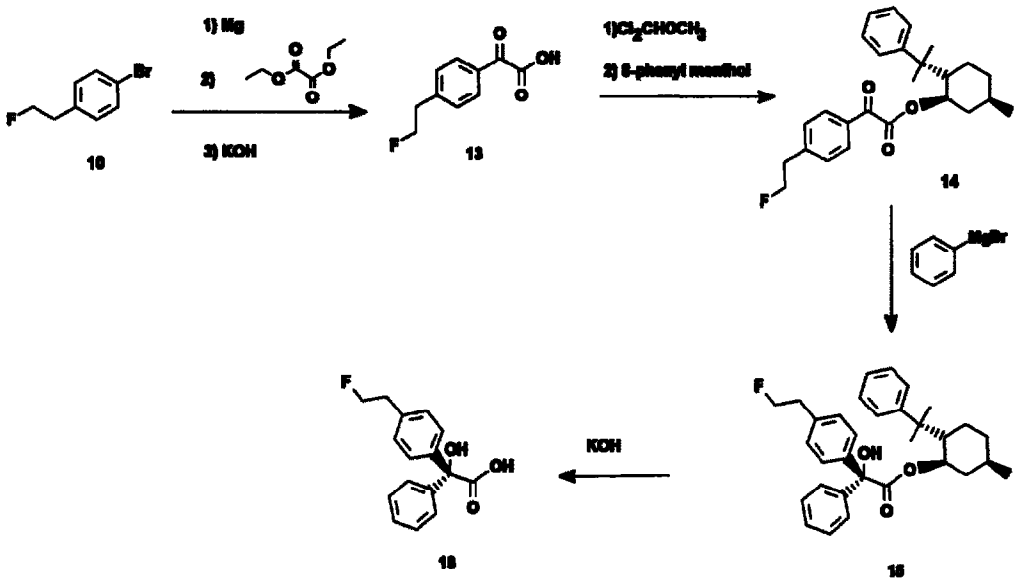
[a] Determined from product mixture prepared by the aryllithium addition.

Basic hydrolysis of the ester provided (S)-hydroxyethylbenzilic acid 9 (Scheme 2). By chiral HPLC, the (S)-benzilic acid obtained from the enantioselective synthesis eluted after the enantiomeric acid obtained by crystallization as the quinidine salt (Table 1, entries 1 and 2). Therefore, the assignment of absolute configuration of hydroxyethylbenzilic acid resolved by the crystallization method of Cohen *et al.* as (R) is consistent with the results of the enantioselective synthesis.[3] Utilizing the same enantioselective synthetic method, the (S)-enantiomer of fluoroethylbenzilic acid was prepared (Scheme 3). In this case the addition to the chiral ester 7 produces less than 5 % of the (R)-stereogenic center. The retention time for the homochiral benzilic acid on the HPLC column is recorded in Table 1. The minor (R)-enantiomer is not detected on the chiral HPLC column. The order of elution of the enantiomers is (R) followed by (S).



Scheme 3

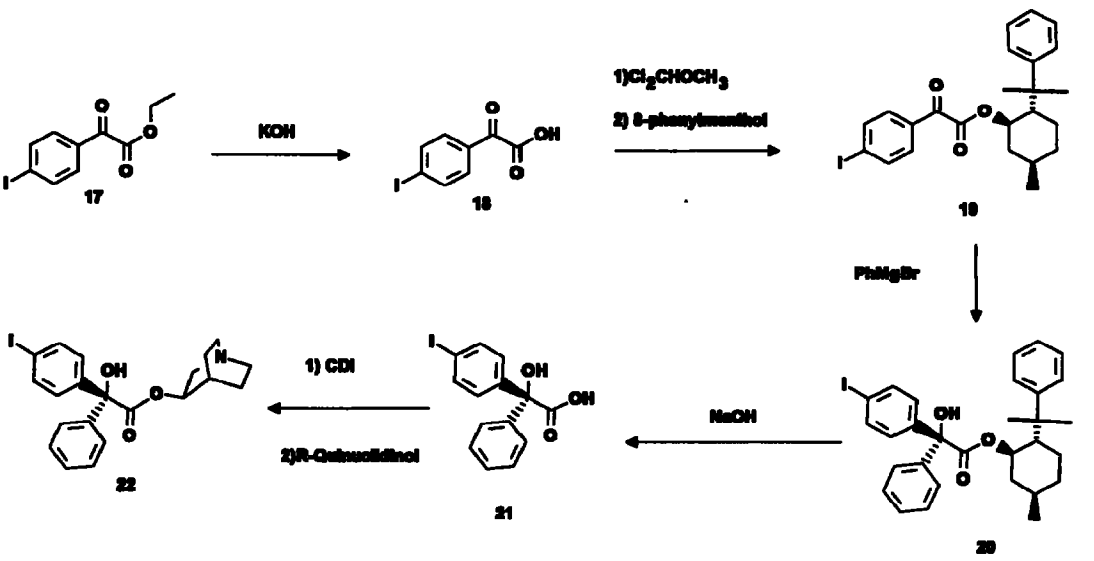
Synthesis of (R) benzilic acids. In order to prepare the opposite configuration of the stereogenic center using the same chiral auxiliary, the appropriately substituted benzoylformic acid must first be prepared. Fluoroethyl benzoylformic acid 13 was prepared in two steps from 4-fluoroethyl-bromobenzene 10 and diethyloxalate. Utilizing the same procedures described above (R)-4-fluoroethylbenzilic acid 16 was prepared (Scheme 4). The (S)-enantiomer is not detected by chiral HPLC.



Scheme 4

Confirmation of the absolute configuration. In order to support the stereochemical assignment of the benzilic acids, the synthesis of (R,R)-IQNB 22 was conducted (Scheme 5). An X-ray crystal structure of (R)-3-acetoxy-quinuclidine methiodide has established the absolute configuration of (R)-quinuclidinol.[11] Therefore, synthesis of (R)-iodobenzilic acid 21 and subsequent coupling with (R)-quinuclidinol should provide (R,R)-IQNB.

Iodobenzoylformic acid 18 was prepared from acylation of iodobenzene with ethyl oxalyl chloride and subsequent hydrolysis of the ethyl ester. Iodobenzoylformic acid 18 was converted to (R)-iodobenzilic acid 21 in the same manner described above for (R)-fluoroethylbenzilic acid (16). Coupling of (R)-iodobenzilic acid 21 with (R)-quinuclidinol yielded (R,R)-IQNB 22 which exhibited identical chromatographic properties with an authentic sample of (R,R) IQNB obtained from Nordion International. The ability of the chromatographic method to separate the two diastereomers (R,R/S,S and R,S/S,R) was demonstrated by separation of the two diastereomers of racemic IQNB. The two diastereomers were separated on an AXXIOM C-18 column (4.6 x 250 mm) using acetonitrile and a buffer (see experimental). The (R,R)-diasteromer eluted at 26.2 min while the (R,S)-diastereomer eluted at 28.6 min.



Scheme 5.

CONCLUSIONS

The enantioselective synthesis provides, as expected, iodobenzilic acid; which, upon conversion to (R,R)-IQNB, is identical to a sample of (R,R)-IQNB obtained from Nordion International. The synthesis of the authentic sample of (R,R)-IQNB is based on the methods described by Cohen.[3]

The assignment of the absolute configuration at the bis-benzilic center is consistent with both the expected configuration from the enantioselective method of Whitesell and the crystallization method of Cohen. Cohen assigned the absolute configuration based on the biological activity of the final products. Whitesell based absolute configuration on configurations of known compounds.

Thus, the enantioselective method of Whitesell provides a method to the synthesis of both enantiomers of fluoroalkyl benzilic acids.

EXPERIMENTAL

General. ^{1}H-, ^{19}F- and ^{13}C-NMR were performed on a Varian VXR-200 NMR spectrometer at 200, 188, and 50 MHz respectively. The samples were dissolved in $CDCl_3$, unless otherwise stated, and the data are reported in δ units. Gas Chromatography-Mass Spectrometry (GCMS) analyses were performed on a Hewlett Packard 5880 GC coupled with a Hewlett-Packard 5790B Mass Selective Detector. The GC conditions used a 12 m HP-1 column with a head pressure of 125 kPa, and initial oven temperature of 100 °C for two minutes, then programmed at 15 °C/min to 250 °C unless otherwise stated. Microanalyses were performed by Galbraith

Laboratories, Knoxville, TN, or by Atlantic Microlabs, Inc. Norcross, GA. CIMS utilized NH_3 as the reagent gas. High resolution electron impact mass spectrometry and CIMS were performed by the Laboratory of Analytical Chemistry, National Institutes of Diabetes, Digestive, and Kidney Diseases.

Chromatography. HPLC separation of the 8-phenylmenthyl esters reported in Table 2 utilized a Beckman ODS C-18 column (4.6 x 250 mm) eluting with CH_3CN and water. HPLC separation of the diastereomers of IQNB utilized an Axxiom C-18 column (4.6 x 250 mm) eluting with 70 % CH_3CN and 30 % buffer (5mM NaH_2PO_4, 5 mM Et_3N, pH not adjusted). The Chiral HPLC separation of the benzilic acid analogs (Table 1) utilized a Chiral Pak WH (Diacel Chemical Industries) (4.6 x 50 mm) eluted with 10 % methanol and 90% 1 mM $CuSO_4$.

Syntheses. 3-(p-Bromophenyl)propan-1-ol[12] and (R)-quinuclidinol[13] were prepared according to literature methods.

General procedure for t-Butyldimethyl silyl ethers. A solution of t-butyldimethylchlorosilane in DMF was added to a solution of bromophenylalkyl alcohol and imidazole in DMF. The solution was stirred overnight. The solution was then diluted with water and extracted with hexane. The hexane was dried and evaporated. The residual oil was eluted through a short flash column (50 mm column, 3 inches of silica gel) with hexane in order to remove unreacted alcohol. The hexane was evaporated to yield the product as an oil. The product may be further purified by Kugelrohr distillation.

1-(t-Butyldimethylsilyloxy)-2-(4-Bromophenyl)ethane **1.** From t-butyldimethylchlorosilane (8.42 gm, 55.9 mmol), imidazole (6.7 gm, 99.5 mmol), and 4-bromophenethyl alcohol (10 gm, 49.7 mmol), one obtains the title product 1 after Kugelrohr distillation (14.4gm, 92%). ^{1}H-NMR 7.41 (d, J= 6.5 Hz, 2H), 7.28 (d, J=6.5 Hz, 2H), 3.79 (t, J=7 Hz, 2H), 2.78 (t, J=7 Hz, 2H), 0.88 (s, 9H), 0.0 (s, 3H). ^{13}C-NMR 138.22, 131.11, 130.82, 119.8, 63.9, 38.8, 25.8, 25.6, 18.2, -5.4. GCMS 7.62 min 259(91), 257(89), 185(22), 183(21), 177(45), 75(100). Anal. Calcd for $C_{14}H_{23}BrOSi$: C, 53.33; H, 7.35; Br, 25.34. Found C, 53.44; H, 7.50; Br, 24.02.

1-(t-Butyldimethylsilyloxy)-3-(4-Bromophenyl)propane **2.** From t-butyldimethylchlorosilane (3.99 gm, 26.47 mmol), imidazole (3.22 gm, 47.38 mmol), and 3-(4-Bromophenyl)propan-1-ol (5.09 gm, 23.69 mmol), one obtains the title product, 3 after the flash column (5.84 gm, 75%). Because the starting alcohol contains some debrominated material, the product also contains this impurity (about 10 %). The product was used in Grignard reactions without additional purification.

GCMS 8.527 min. 315 (0.2), 273(34), 271(33), 89(100) ^{1}H-NMR 7.4 (d, J=5Hz, 2H), 7.06 (d, J=5Hz, 2H), 3.62 (t, J=6 Hz, 2H), 2.63 (t, J= 6 Hz, 2H), 1.70-1.90 (m, 2H), 0 92 (s, 9H), 0.08 (s, 3H).

4-Bromophenethyl fluoride **10.** A solution of 4-bromophenethyl alcohol (9.74 gm, 48.5 mmol) and pyridine (7.8 mL, 97 mmol) in 100 mL CH_2Cl_2 was added to an ice cooled solution of triflic anhydride (27.5 g, 97 mmol) over 50 min. After the addition was completed, the solution was stirred for an additional 2 h. The

solution was partitioned with cold water and the organic phase was dried and evaporated. The intermediate triflate was characterized quickly by ^{1}H-NMR and used without further purification.The organic phase was evaporated, the residue taken up in CH_3CN, and Me_4NFHF (16.46 gm, 145 mmol) was added. The mixture was stirred at room temperature for 1 h. The solution was diluted with water and extracted with hexane (2 x 60 mL). The organic layer was dried and evaporated. The residue was subjected to a short flash column (silica gel, hexane). The fractions were concentrated to give the final product, **10**, as an oil (9.39 gm, 95%).

^{1}H-NMR 7.40-7.45 (m, 2H), 7.12-7.25 (m, 2H), 4.60 (dt, J= 47, 6 Hz, 2H), 2.96 (dt, J= 24, 6 Hz, 2H). ^{13}C-NMR 136.25 (d, J= 5 Hz), 131.6, 130.7, 120.6, 83.7 (d, J= 169 Hz), 36.38 (d, J=20 Hz) GCMS 2.859 min 204(31), 202 (32), 172 (100), 170(100), 90(43). Anal. Calcd for C_8H_8BrF. C, 47.32; H, 3.97; Br 39.35. Found C, 47.66; H, 4.14; Br, 39.19.

t-Butyl benzoylformate. Benzoylformic acid (25 gm, 166.7 mmol) was treated with α,α-dichloromethyl methyl ether (16.56 mL, 183 mmol) at 50 °C for one hour. CH_2Cl_2 (100 mL) was added and the solution was purged with nitrogen for 2 min. The solution was transfered via addition funnel into an ice cooled solution of Et_3N (23 mL, mmol) and t-butanol (16.75 mL, 166.7 mmol). After stirring 3 h, the solution was partitioned with water and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried and evaporated. The residue was subjected to distillation in a Kugelrohr (approximately 1 mm, 130 °C) in several batches to yield the final product as an oil (19.74 g, 57 %).

^{1}H-NMR 8.04-7.87 (m, 2H), 7.69-7.55 (m, 1H), 7.55-7.42 (m, 2H), 1.63 (s, 9H). ^{13}C-NMR 186.4, 163.6, 134.5, 132.4, 129.8, 128.7, 84.6, 28.0. GCMS 5.04 min 151(0.08), 105(59), 77(37), 57(100). Anal. Calcd for $C_{12}H_{14}O_3$ C, 69.89; H, 6.84. Found C, 69.61; H, 6.83.

***[R] α-Hydroxy-α-(4-[2-hydroxyethyl]phenyl) benzeneacetic acid* 5.** t-Butyl benzoylformate (2.34 g, 11.2 mmol) in 10 mL THF at -78 °C was treated with a slight excess of the Grignard reagent (prepared from the silyl protected bromophenethyl alcohol, **1**, (3.8 g, 12.06 mmol) and Mg (355 mg, 14 mmol) in 10 mL THF at reflux). The addition reaction was allowed to stir overnight and then quenched with 200 mL 10% NH_4Cl. The mixture was extracted with $CHCl_3$ (3 x 100 mL). The combined organic layers were dried and evaporated. The residue was dissolved in 20 mL CH_3CN, and concentrated HF (2 mL) was added. The solution was stirred for 75 min. Water (100 mL) was added and the solution neutralized with aqueous KOH. The aqueous mixture was extracted with two 100 mL portions of $CHCl_3$. The organic layers were dried and evaporated. The residue was subjected to flash chromatography (40 mm column, 1:1 ethyl acetate: hexane). The product fractions were collected and concentrated to yield 3.06 g of **3**, 83% of material which by GC was at least 90 % pure. The material was used without further purification. GCMS 11.56 min 227(100), 149(15), 105(61). ^{1}H-NMR (crude) 7.50-7.25 (m, 7H), 7.20 (d, J= 5Hz, 2H), 3.85 (m, 2H an impurity under this signal), 2.86 (t, J= 4 Hz, 2H), 1.44 (s, 9H).

The product was taken up in ethanol (15 mL). Water (10 mL) and KOH (3 mL of 8 M) were added, and the solution was heated at 80 °C for 4 hr to effect the hydrolysis. The solution was diluted with water (50 mL), acidified with concentrated HCl and extracted with $CHCl_3$ (2 x 30 mL). The combined organic layers were

dried and evaporated. The residual solid 5 (2.152 g) was characterized by ^{1}H NMR, and CIMS and observed to contain a small amount of ethanol. ^{1}H-NMR ($CDCl_3$ with a few drops of DMSO-d_6) 7.55-7.15 (m, 9H), 3.8 (t, J= 4 Hz, 2H), 2.85 (t, J= 4 Hz, 2H).

The acid 5 was subsequently added to a hot solution of quinidine (2.571 g) in ethyl acetate (35 mL). The resulting solids were recrystallized from ethyl acetate three times to effect the resolution. The (R)-enantiomer quinidine salt was obtained (1.55 g, 32%) (mp 178-183 °C with decomposition).

^{1}H-NMR (acetone-d_6) 7.59-7.45(m, 2H), 7.44-7.27 (m, 5H), 7.27-7.15 (m, 2H), 3.77(t, J= 7 Hz, 2H), 2.82(t, J= 7 Hz, 2H). ^{13}C-NMR (acetone-d_6) 174.9, 143.6, 141.2, 139.5, 128.8, 128.1, 127.9, 127.8, 127 7, 80.9, 63.3, 39.3. CIMS 290 (M+18, 65), 244(100). Anal. Calcd for $C_{36}H_{40}N_2O_6$ * 1/2 $C_4H_8O_2$. C, 71.23; H, 6.92; N, 4.37. Found C, 71.27; H, 7.06; N, 4.23.

***(R)-Hydroxypropylbenzilic acid, Quinidinine salt* 6.** Ethyl benzoylformate (1.603 g, 8.99 mmol) in 15 mL THF at -78 °C was treated with a slight excess of the Grignard reagent (prepared from the silyl protected 3-(4-bromophenyl)propan-1-ol 2 (3 g, 9.12 mmol) and Mg (274 mg, 11 mmol) in 7 mL THF at reflux). The addition reaction was allowed to stir 2 h and then quenched with 100 mL 10% NH_4Cl. The mixture was extracted with $CHCl_3$ (2 x 40 mL). The combined organic layers were dried and evaporated. The residue was dissolved in 50 mL CH_3CN and 5 mL concentrated HF was added. The solution was stirred for 2 h. Water (100 mL) was added and the solution neutralized with aqueous K_2CO_3. The aqueous mixture was extracted with two 40 mL portions of $CHCl_3$. The organic layers were dried and evaporated. The residue was subjected to flash chromatography (40 mm column, 1:1 ethyl acetate: hexane). Only one fraction contained desired product which was nearly free of the side product. The fractions containing product were collected and concentrated to yield 1.22 g, of material which by GC contained two components. A small amount of the two components were separated by HPLC (C-18 column, 60 % ACN, 40% water). GCMS of the first peak was consistent with the desired product (11.948, 241 (100), 195 (40), 163 (15). The second peak showed a mass spectrum consistent with a benzil product, which would arise if Grignard addition occured at the ester carbonyl (11.973 min 268(0.4,M+), 163(100), 105 (24). ^{1}H-NMR (mostly upper fraction from Flash column) 7.55-7.04 (m,), 4.37-4.27 (m, almost q), 3.66 (brt, J=6 Hz), 2.70 (t, J= 6 Hz), 1.95-1.75 (m,), 1.25 (t, J=8 Hz).

The crude product 4 was taken up in ethanol (3 mL). Water (3 mL) and NaOH (445 mg) were added, and the solution was heated at 75 °C overnight to effect the hydrolysis. The solution was diluted with water (25 mL) and extracted with hexane. The aqueous layer was acidified with concentrated HCl and extracted with $CHCl_3$ (2 x 20 mL). The combined organics were dried and evaporated to provide 822 mg of oil. The material was subjected to flash chromatography (silica gel, 1:1 ethyl acetate:hexane containing 0.5 % HOAc). Product (6) was obtained by concentration of the fractions to provide 552 mg of oil

The acid 6 in 15 mL ethyl acetate was subsequently added to a hot solution of quinidine (658 mg) in ethyl acetate (15 mL) This solution was allowed to stand overnight. The resulting solids were recrystallized from ethyl acetate to effect the resolution. The pure (R) isomer quinidine salt was isolated 244 mg (mp 188-190 °C with decomposition). To assay the chiral purity of the salt, a portion was partitioned between chloroform and

1 N HCl. The organic phase was concentrated and assayed by chiral HPLC. The free acid was also characterized by NMR and CIMS.

^{1}H-NMR(acetone-d_6) 7.58-7.45 (m, 2H), 7.45-7.25(m, 5H), 7.25-7.12(m, 2H), 3.57 (t, J=6.5 Hz, 2H), 2.75-2.49 (m, 2H), 1.91-1.68 (m, 2H). ^{13}C-NMR (acetone-d_6) 174.8, 143.6, 142.3, 140.9, 128.2, 128.1, 127.8, 127.7, 80.8, 61.2, 34.9, 31.9. CIMS 304 (M+18, 85), 258 (100). Anal of Quinidine salt. Calcd for $C_{37}H_{42}N_2O_6$ * 1/2 C_4H_8O: C, 71.54; H, 7.08; N, 4.28. Found C, 71.25; H, 7.16; N, 4.15.

***(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl) cyclohexyl benzoylformate* 7.** Benzoylformic acid (855 mg,5.7 mmol) is heated with α,α-dichloromethyl methyl ether (515 µL, 5.7 mmol) at 50 °C for one hour under argon. CH_2Cl_2 (10 mL) is added and the solution purged with argon for one minute. This solution is poured into an addition funnel and added dropwise to an ice cooled solution of 8-phenylmenthol (1.009 g, 4.324 mmol) and Et_3N (834 µL, 6 mmol) over approximately 15 min. The resulting mixture was stirred for twenty minutes, the ice bath removed, and the mixture stirred overnight. The solution was washed with 15 mL of water, dried (Na_2SO_4), and evaporated. The residual oil was purified by flash chromatography (40 mm column, 10% EtOAc in hexane). To provide 1.36 g (86 %) of 7 as an oil which crystallized upon standing. An analytical sample was recrystallized from ethanol (mp 86.4-89.4 °C).

^{1}H-NMR ($CDCl_3$) 7.95 (d, 2H), 7.6-7.1 (m, 1H), 7.45-7.60 (m, 2H), 7.2-7.3 (m, 2H), 6.95-7.20 (m, 3H), 5.05 (dt, 1H), 2.0-2.25 (m, 2H), 1.55-1.75 (m, 3H, 1.4 (s, 3H), 1.3 (s, 3H), 1.0-1.3 (m 2H), 0.95 (d, 3H). ^{13}C-NMR 185.76, 162.72, 150.22, 134.45, 132.69, 130.04, 128.64, 127.95, 125.48, 125.27, 77.506, 50.60, 41.43, 40.04, 34.41, 31.45, 27.56, 26.96, 26.10, 21.70. GCMS 100/2/15/250 13.82 min. 364 (M+, 0.3), 214 (11),119(100), 105 (92) EIMS 364(2), 214(30), 119(100). HREIMS Calculated for $C_{24}H_{28}O_3$ 364.2038. Observed 364.2055. Analysis. Calculated for $C_{24}H_{28}O_3$ C, 79.09; H, 7.74. Found C, 78.73; H, 7.80

***(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl) cyclohexyl-[S]-α-hydroxy-α-(4-[2-hydroxyethyl]phenyl) benzeneacetate* 8.** 4-Bromophenethanol, t-butyldimethylsilyl ether, 1 (787 mg, 2.5 mmol) was dissolved in 2 mL THF and added to magnesium turnings (75 mg). A few crystals of iodine were added and the mixture heated to reflux. After 90 minutes the reaction was removed from the heating bath and allowed to cool. THF (2 mL) was added. Approximately half of the solution (2.5 mL) was then added dropwise to a solution of 8-phenylmenthyl benzoylformate 7 (364 mg, 1 mmol) dissolved in 2 mL THF and cooled in a dry ice/ 2-propanol bath. The reaction solution was allowed to warm up over one hour and then allowed to stir at room temperature for two hours. Then the mixture was poured into 20 mL 10 % NH_4Cl and extracted with 2 x 15 $CHCl_3$. The organic layer was dried and evaporated. The resulting oil was transferred with 4 x 1 mL CH_3CN into a plastic vial. HF (400 µL) was added and the resulting solution was stirred at room temperature for 2 h. This was then poured into potassium carbonate and extracted with 2 x 5 mL $CHCl_3$. The organic phase was dried and evaporated. The resulting oil was subjected to flash chromatography (30 mm, 1:1 EtOAc:hexane) to yield starting keto ester (7) (113 mg) and product 8 (349 mg) which was found to contain phenethyl alcohol. This impure product (256 mg) was heated at 80 °C at 1 mm for four hours. Product 8 (190 mg) was obtained whose NMR indicated that the impurity was no longer detectable.

^{1}H-NMR 7.1-7.45 (m, aromatic cluster), 4.89 (dt, 1H), 3.84 (brt, J= 6 Hz, 2H), 3.05 (s, 1H), 2.86 (t, J= 6 Hz, 2H), 1.90-2.15 (m, 2H), 1.5-1.75 (m, 4H), 1.1 (s, 3H), 1.0 (s, 3H), 0.85 (d, 3H) ^{13}C-NMR 172.10, 150.97, 141.87, 140.15, 138.17, 128.53, 128.06, 127.86, 127.71, 127.50, 127.10, 125.25, 125.20, 80.71, 78.15, 63.48, 50.03, 40.98, 39.59, 38.76, 34.38, 31.32, 26.87, 26.74, 26.02, 21.68. CIMS 504 (M+ 18) HREIMS Calcd for $C_{32}H_{38}O_4$ 486.2770. Observed 486.2744.

***[S]-α-Hydroxy-α-(4-[2-hydroxyethyl]phenyl) benzeneacetic acid* 9.** 8-Phenylmenthyl hydroxyethylbenzilate 8 (179 mg, 368 μmol) was dissolved in 6 mL ethanol. Water (1.2 mL) and 275 μL of 45% KOH were added. The resulting solution was heated at 75 °C for 4 hours. Water (10 mL) was added and the mixture extracted with 2 x 10 mL $CHCl_3$. The aqueous layer was acidified and extracted with 2 X 10 mL EtOAc:CHCl3 (1:1). The organic layers were dried and evaporated to provide 100 mg of oily product 9.

^{1} H-NMR (acetone-d_6) 7.56-7.44 (m, 2H), 7.25-7.44(m, 5H), 7.25-7.11 (m, 2H), 3.76(t, J=7, Hz, 2H), 2.80 (t, J= 7 Hz). ^{13}C-NMR (acetone-d_6) 174.74, 143.38, 141.00, 139.26, 128.61, 127.91, 127.70, 127.54, 127.45, 80.72, 63.03, 39.06. CIMS 290(M+18, 2), 272 (30), 244 (100).

***(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl) cyclohexyl-[S]-α-Hydroxy-α-(4-[2-fluoroethyl]phenyl) benzeneacetate* 11.** A flask was charged with magnesium (162 mg, 6.75 mmol) and filled with argon using a Firestone valve. A portion (1 mL) of a solution of 4-bromophenethyl fluoride, 10, (1.03 gm, 5.07 mmol) in 5 mL THF was added followed by a crystal of iodine. The mixture was sonicated. Within two minutes the iodine color dissipated. The remainder of the bromoarene solution was added portionwise. Within 30 min, the reaction seemed to have subsided; the sonication was stopped. A solution of 8-phenylmenthyl benzoylformate, (7), (1.375 gm, 3.77 mmol) in 10 mL THF was cooled in a dry ice/acetone bath. The Grignard solution was added over 3-5 min. The reaction was stirred for 40 min and then the cooling bath removed. The solution was allowed to stir an additional 90 min. The reaction was then poured into 50 mL 10% NH_4Cl and extracted with two portions of EtOAc (30 mL). The combined organic layers were dried and concentrated. The residue was subjected to flash chromatography (50 mm, 10 % EtOAc/Hexane). The product, 11, was isolated (1.295 g, 70%).

^{1}H-NMR 7.13-7.44 (m, 9H), 7.10 (s, 5H), 4.88 (dt J= 10,4, 1H), 4.65 (dt, J=47, 6 Hz, 2H), 3.03 (dt, J= 23, 6 Hz, 2H), 2.89 (s, 1H), 1.95-2.07 (m, 2H), 1.26-1.64 (m, 2H), 1.08 (s, 3H), 0.99 (s, 3H), 0.83-1.01 (m, 2H), 0.820 (d, J= 6 Hz, 3H). ^{13}C-NMR 171.95, 150.94, 141.88, 140.34, 136.74, 136.61, 128.40, 127.99, 127.78, 127.63, 127.45, 127.15, 127.05, 125.17, 125.12, 83.80 (d, J= 165 Hz), 80.61, 78.07, 50.00, 40.93, 39.51, 36.44 (d, J= 20 Hz), 34.36, 31.27, 26.80, 25.77, 21.60. ^{19}F-NMR -215.45 (tt, J= 47, 17 Hz). CIMS 506 (M+18) EIMS 488(1), 229 (80), 105(100) HREIMS Calcd for $C_{32}H_{37}FO_3$ 488.2726. Observed 488.2710.

***[S]-α-Hydroxy-α-(4-[2-fluoroethyl]phenyl) benzeneacetic acid* 12.** The 8-phenylmenthyl ester, 11 (1.2 g, 2.46 mmol) was dissolved in 36 mL ethanol. Water (7 mL) and concentrated KOH (45 %, 2.5 mL) were added and the solution heated at 85 °C for 60 minutes at which time TLC indicated completion of the reaction. Heating was discontinued; the solution was acidified with 50 mL of 1N HCl, and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried and concentrated. The residue was subjected to flash

chromatography (10% EtOAc in hexane, followed by EtOAc:hexane:HOAc; 5:94.5:0.5). The product 12 was isolated as an orange oil which solidified on prolonged standing (474 mg, 70%). mp 111-113 °C.

^{1}H-NMR ($CDCl_3$/DMSO) 7.10-7.60 (m, 9H), 4.61 (dt, J= 47, 7 Hz, 2H), 2.99 (dt, J= 24, 6 Hz). ^{13}C-NMR 142.33, 140.83, 136.49, 136.36, 128.34, 127.74, 127.52, 127.24, 127.02, 83.76 (d, J=169 Hz), 80.25, 36.32 (d, 20 Hz). CIMS 292 (M+18). Anal. Calcd for $C_{16}H_{15}FO_3$. C, 70.06; H, 5.51. Found C, 69.62; H, 5.55.

4-(2-Fluoroethyl)benzoyl formic acid **13.** Fluoroethylphenyl magnesium bromide was prepared utilizing sonication as described above from fluoroethylphenyl bromide **10** (5 g, 24.6 mmol) in 25 mL THF. This solution was added dropwise to a solution of diethyl oxalate (7 mL, 50 mmol) in 40 mL THF which was cooled in dry ice/acetone bath. After 40 min the cooling bath was removed. After an additional hour the solution was poured into 250 mL of 10% NH_4Cl. The mixture was extracted with 3 portions of chloroform (200 mL), the organic layers dried, and the solvent evaporated. The residue was subjected to Kugelrohr distillation which removed some of the excess diethyloxalate.

The material which was collected at 150 °C and 0.5 mm (4.38 g, containing approximately 3 gm desired ethyl ester by NMR) was mixed with 20 mL of 2N NaOH and stirred for 30 minutes. Precipitate formed rapidly. The mixture was acidified with 100 mL 1 N HCl and extracted with three protions of $CHCl_3$. The organic layers were dried and concentrated. The solid residue was crystallized from carbon disulfide in an ice bath. An analytical sample was further purified by flash chromatography (ethyl acetate:hexane, 1:1, with 4 % acetic acid) to provide solid **13**. mp 46-49 °C.

^{1}H-NMR (DMSO-d_6) 7.90 (d, J=8 Hz, 2H), 7.54 (d, J=8 Hz, 2H), 4.71 (dt, J=48, 6 Hz, 2H), 3.11 (dt, J=26, 6 Hz, 2H). CIMS 214 (M+18). Anal. Calcd for $C_{10}H_9FO_3$ C, 61.22; H, 4.62. Found C, 61.30; H, 4.67.

(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl) cyclohexyl 4-(2-fluoroethyl)benzoylformate **14.** Fluoroethylbenzoylformic acid **13** (412 mg, 2.1 mmol) was treated with Cl_2CHOCH_3 (208 µL) and 1 mL CH_2Cl_2 and heated at reflux for 2 h. CH_2Cl_2 (2 mL) was added and the solution purged for 1 min with argon. This solution was added dropwise to an ice cold solution of 8-phenylmenthol (436 mg, 1.87 mmol) and Et_3N (556 uL, 4 mmol) in 5 mL CH_2Cl_2. After 60 min, the reaction solution was poured into water (20 mL), acidified with HCl, and the layers separated. The aqueous layer was extracted with an additional 20 mL CH_2Cl_2. The combined organic layers were dried and concentrated. The residue was subjected to flash chromatography, first with 10 % EtOAc/hexane which failed to separate the product from the starting material, and finally with 1:1 CH_2Cl_2: hexane. The product, **14**, was isolated as an oil (404 mg, 63%).

FTIR (neat) 2959, 2920, 2872, 1726, 1686, 1211. ^{1}H-NMR 7.95 (d, J= 8 Hz ,2H), 7.40 (d, J= 8 ,2H), 6.95-7.30 (m, 5H), 5.05 (dt, J= 9, 4 Hz 1H), 4.7 (dt, J= 47, 6 Hz 2H), 3.1 (dt, J= 25, 6 Hz, 2H), 1.95-2.20 (m, 2H), 1.35 (s, 3H), 1.30 (s, 3H), 0.8-1.6 (m, 6H), 0.9(d, J= 6 Hz, 3H). ^{13}C-NMR 185, 150, 144, 131, 130, 129, 127, 125, 125, 83.1(d, J=270), 77.4, 50.4, 41.3, 39.9, 36.9(d, J=21 Hz), 34.3, 31.3, 29.6, 27.5, 26.8, 25.9, 21.6. CIMS 428 (M + 18). HREIMS Calcd for $C_{26}H_{31}FO_3$ 410.2257. Observed 410.2268.

(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl) cyclohexyl-[R]-α-Hydroxy-α-(4-[2-fluoroethyl]phenyl) benzene acetic acid **15.** Keto ester, 14 (162 mg, 395 μmol) was dissolved in 3 mL THF and cooled in a dry ice/acetone bath. Phenyl magnesium bromide (0.6 mL, 1M) was added dropwise over 2 min. At one hour the cold bath was removed. 3 h later the reaction solution was poured into 10 mL of 10% NH_4Cl. The mixture was extracted with $CHCl_3$ (2 x 15 mL). The organic layers were combined, dried and concentrated. The residue was subjected to flash chromatography (20 mm, 10% EtOAc/hexane). The product, 15, was isolated as an oil (161 mg, 83%).

1H-NMR 7.49-7.50 (m, 2H), 7.30-7.47 (m, 5H), 7.08-7.29 (m, 7H), 4.87 (dt, J= 9, 4Hz, 1H), 4.5 (dt, J= 48, 7 Hz, 2H), 2.96 (t, J=7 Hz, 1H), 2.85 (t, J= 7Hz,1H), 1.95-2.2 (m, 2H), 0.80-1.7 (m, 4H), 1.07 (s, 3H), 0.98 (s, 3H), 0.84 (d, J=6 Hz, 3H). 19F-NMR -215.19 (sept, J=23 Hz). 13C-NMR 171.9, 150.87, 141.79, 140.47, 136.50(d, J=6), 128.32, 127.95, 127.77, 127.73, 127.30, 127.12, 125.06, 80.56(d, J= 169 Hz), 80.56, 78.05, 50.01, 40.92, 39.45, 36.32(d, J= 20 Hz), 34.34, 31.22, 26.77, 25.71, 21.55). EIMS 488(2), 229(100). HREIMS Calcd for $C_{32}H_{37}FO_3$ 488.2726, Observed 488.2718.

[R]-α-Hydroxy-α-(4-[2-fluoroethyl]phenyl) benzene acetic acid **16.** 8-phenylmenthyl ester, 15, (840 mg, 1.72 mmol) was dissolved in 36 mL ethanol. Water (7 mL) and KOH (8 M, 2.1 mL) was added and the solution heated at 80 °C for 1 h. Aqueous HCl (50 mL, 1N) was added and mixture extracted with EtOAc (2 x 50 mL). The combined organic layers were dried and concentrated. The residue was partitioned between NaOH (1N) and $CHCl_3$. The aqueous layer was acidified and extracted with 1:1 EtOAc:$CHCl_3$. The final organic layer was dried and evaporated to yield the product 16 (392 mg, 83 %) mp 113-115 °C.

^{1}H-NMR 7.30(m, 7H), 7.2-7.3 (m, 2H), 4.62(dt, J= 48, 5 Hz, 2H), 3.02 (dt, J=23, 5 Hz, 2H). ^{13}C-NMR 178.18, 140.97, 139.45, 137.36 (J=5 Hz), 128.74, 128.30, 128.16, 127.45, 127.17, 83.66 (J= 169 Hz), 80.88, 36.39 (J=21 Hz). CIMS 292 (M+18). EIMS 274 (0.1)229 (100). HREIMS Calcd for $C_{16}H_{15}FO_3$ 274.1005 Observed 274.1009. Anal. Calcd for $C_{16}H_{15}FO_3$ C, 70.06; H, 5.51. Found C,69.50; H, 5.53.

4-Iodobenzoylformic acid **18.** $AlCl_3$ (8 g, 60 mmol) and Iodobenzene (11 g, 54 mmol) were added to 50 mL CS_2. $ClCOCO_2Et$ (6.7 mL, 60 mmol) was added dropwise over 15 minutes. The resulting reddish mixture was stirred for 3 h. The mixture was poured into 200 mL ice and 60 mL concentrated HCl. The layers were separated and the aqueous layer extracted with two portions of CH_2Cl_2. The combined organic layers were washed with 1 N HCl, 0.1 N NaOH, and then dried. The residue was subjected to flash chromatography (50 mm 10% EtOAc/hexane). The product was isolated as an oil (4 5 g, 27%), characterized by NMR and used in the next step. 1H-NMR 7.89 (d, J=9Hz, 2H), 7.73 (d, J=9Hz, 2H), 4.45 (q, J= 7Hz, 2H), 1.42 (t, J=7Hz, 3H). 13C-NMR 163.3, 138.45, 103.80, 62.71, 14.28.

The ester 17 was mixed with 11.1 mL of 2N NaOH. A solid formed immediately. After stirring 1h, water (20 mL) and 1N HCl (23 mL) were added The mixture could not be successfully extracted. The solids were filtered and triturated with two portions of hexane. A 2.5 gm sample was successfully recrystallized from water to give 2 gm, 50 % of 18. mp 113-119 °C.

^{1}H (DMSO) 8.04 (d, J= 9Hz, 2H), 7.71 (d, J=9 Hz, 2H). ^{13}C (DMSO) 165.59, 138.44, 131.09, 104.66. Anal. Calcd for $C_8H_5O_3I$. C, 34.81; H, 1.83; I, 45.97. Found C, 35.12; H, 1.87; I, 45.75.

***(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl) cyclohexyl-[R]-α-hydroxy-α-(4-iodophenyl) benzeneacetate* 19.** Iodobenzoylformic acid 18 (828 mg, 3 mmol) was treated with dichloromethyl methyl ether (271 μL, 3 mmol) in 2 mL CH_2Cl_2 and 100 μL dichloroethane at 80 °C for 2h. An additional 2 mL dichloroethane was added and the solution purged with argon for one minute. This solution was added to a solution of 8-phenylmenthol (613 mg, 2.64 mmol) and triethylamine (695 μL, 5 mmol) in CH_2Cl_2 (10 mL) and allowed to stir overnight. The solution was partitioned with water, washed with 1 N NaOH, dried and concentrated. The residue was subjected to flash chromatography(10% EtOAc/hexane). 19 was isolated as an oil. (685 mg, 53%).

^{1}H NMR 7.87 (d, J= 9 Hz,2H), 7.66 (d,J= 9 Hz, 2H), 7.13-7.25 (m, 2H), 6.93-7.12 (m, 3H), 5.00 (dt, J=10,5 Hz, 1H), 2.02-2.13 (m, 2H), 2.68 (s, 3H), 2.56 (s, 3H), 1.07-1.71 (m, 5H), 0.91 (d, J=5 Hz, 3H), 0.8-0.95 (m, 2H). ^{13}C NMR 184, 161.8, 150.2, 137.9, 131.8, 131.1, 127.8, 125.2, 125.1, 103.0, 77.5, 50.3, 41.3, 39.8, 34.2, 31.3, 26.7, 26.5, 21.6. EIMS 490 (3), 119(100). HREIMS Calcd for $C_{24}H_{27}IO_3$ 490.1004, Observed 490.1005.

***(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl) cyclohexyl -[R]-α-hydroxy-α-(4-iodophenyl) benzeneacetate* 20.** A solution of the above ketoester 19 (615 mg, 1.26 mol) was dissolved in 10 mL THF and cooled in a dry ice/acetone bath. A solution (1.9 mL, 1M) of phenylmagnesium bromide was added over 8 min. The reaction was maintained in the dry ice/acetone temperature for 1 h; allowed to warm to room temperature, and stirred an additional 2 h. The solution was poured into 20 mL 10% NH_4Cl and extracted with chloroform (3 x 15 mL). The combined organic layers were dried and evaporated. The residue was subjected to flash chromatography (40 mm, 10% EtOAc/hexane). 20 was isolated as an oil (693 mg, 95%).

^{1}H-NMR 7.50-7.64 (m, 2H), 7.29-7.50(m, 5H), 6.99-7.13 (m, 7H), 4.86 (dt, J= 4, 11 Hz, 1H), 2.01-2.20 (m, 1H), 1.85-2.01 (m, 1H), 1.11-1.77 (m, 5H), 1.08 (s, 3H), 1.05 (s, 3H), 0.69-0.92 (m, 2H), 0.86 (d, J=6 Hz, 3H). ^{13}C-NMR 171.59, 151.45, 142.07, 141.83, 137.12, 129.38, 128.33, 128.27, 128.11, 128.07, 127.32, 125.38, 93.9, 80.7, 78.5, 50.24, 41.16, 39.68, 34.67, 31.57, 27.94, 26.97, 25.12, 21.88. EIMS 568 (50), 309 (100). HREIMS Calcd for $C_{30}H_{33}O_3I$ 568.14744, Observed 568.1415.

***[R]-α-Hydroxy-α-(4-iodophenyl) benzeneacetate* 21.** 8-Phenylmenthyl ester 20 (645 mg, 1.135 mmol) was dissolved in 30 mL ethanol. Water (6 mL) and KOH (1.3 mL, 8 M) were added and the solution heated at 80 ° C for two hours. The solution was concentrated and then partitioned between $CHCl_3$ and NaOH (1N). The basic layer was acidified and extracted with 1:1 - $CHCl_3$:EtOAc. The organic layer was dried and concentrated. The residue was partitioned between $CHCl_3$ and NaOH (1N). The basic layer was acidified and extracted with $CHCl_3$:EtOAc (1:1) . The organic layer was dried and concentrated to yield 21 (336 mg, 83 %).

^{1}H-NMR 7.43-7.70 (m, 2H), 7.29-7.49(m, 5H), 7.14-7.29 (m, 2H). ^{13}C-NMR 178.07, 140.76, 140.70, 137.35, 129.35, 128.68, 128.46, 128.30, 127.325, 127.139, 94.563, 80.85. CIMS 372 (M+18). EIMS 354 (6), 309 (100). HREIMS Calcd for $C_{14}H_{11}O_3I$ 353.9753, Observed 353.9744.

***[R]-Azabicyclo[2.2.2]oct-3-yl-[R]-α-hydroxy-α-(4-iodophenyl) benzeneacetate* 22.** Iodobenzilic acid 21 (216 mg, 610 μmol) was dissolved in 3 mL DMF. Carbonyl diimidazole (104 mg, 641 μmol) was added and the solution stirred for 60 min. Then (R)-quinuclidinol (85 mg, 669 μmol) was added and the solution stirred overnight. NaOH (10 mL, 1N) was added and the mixture extracted with $CHCl_3$. The organic layers were dried and concentrated. The DMF was removed by Kugelrohr and the residue subjected to flash chromatography (20 mm, $CHCl_3$:MeOH:ammonia, 90:9:1). The collected product 22 was crystallized from CH_3CN. (104 mg, 36%). mp 195-197 °C.

^{1}H-NMR 7.65-7.71(m, 2H), 7.21-7.41 (m, 7H), 4.91-4.98 (m, 1H), 3.08-3.20 (dd, J= 15, 2 Hz, 1H), 2.45-2.95 (m, 5H), 1.98-2.00 (m, 1H), 1.24-1.64 (m, 4H). ^{13}C-NMR 173.69, 141.88, 137.12, 135.07, 129.46, 128.22, 128.08, 128.04, 127.25, 121.95, 94.02, 80.75, 74.21, 54.84, 47.03, 46.16, 25.08, 24.15, 19.26. EIMS 463(35), 309(100). HREIMS Calcd $C_{21}H_{22}INO_3$ 462.0644, Observed 463.0622.

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